ON THE USE OF SALVARSAN IN THE TREATMENT OF SYPHILIS

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MUCH has already been written on the subject of the treatment of syphilis by means of salvarsan or, as it is popularly known, "606." The chemical constitution of the new remedy and the methods by which it was discovered have been so often described that it would be mere waste of time to allude to them here, but we think it may be of some value to place on record the results we have obtained by the use of the drug during the last nine months.

Through the kindness of Professor Ehrlich we were enabled to use the remedy since August of last year. At first all our injections were made intramuscularly, but later, owing to a letter we received from Professor Ehrlich we changed the method to an intravenous one. The intravenous method has many advantages. It is much less painful, and enables the patient to get about with perfect comfort in much less time than the older method. Its effect is quicker and more certain, and recurrences are less common.

Since we started the intravenous method we have used several forms of apparatus for the administration of the drug. At first we used what seemed to be the very simplest form of apparatus—namely, a graduated funnel connected with a needle, which was inserted into a vein, the rate of flow being graduated simply by the height of the funnel. The method had been previously described, we believe, in Germany, and has since been described repeatedly with very small alterations. The advantage of the apparatus is its simplicity, while the disadvantage is that unless a very large needle is used the rate of flow is slow, and the operation takes an inordinate time in its performance, while the use of a very large needle is rather disagreeable to the patient. Later we used receptacles for the salt solution and the "606" connected with a needle on the one hand and with a Higginson's syringe on the other, similar in principle to that

which has since been described by Dr. Otto Grünbaum, but this apparatus was rather cumbersome for general use, and since January we have used solely a syringe connected by a three- or four-way tap to a needle and to the receptacles for the salt solution and the "606." A similar apparatus was long ago described for the purpose by Schreiber,[1] but we think that the form we shall describe has several advantages over the original pattern. The chief advantages are these :

1. Between the needle and the syringe there is a long flexible rubber tube, so that any movement of the syringe is not communicated to the needle, and thus damage to the walls of the vein is avoided.

2. The three-way tap is made to fit a "Record" syringe, which is in fairly general use and which has the advantage over the all-glass syringe that while it works perfectly so far as its mechanics is concerned, is not so easily breakable as the all-glass syringe. This may seem to be rather a trifling point, but it is all-important if one goes out to inject a case with "606" with only a single syringe, and if by some mishap the nozzle of the all-glass syringe breaks and leaves one helpless.

3. Between the needle and the syringe there is arranged a small piece of wide-bore glass tube, which serves when one holds it (as one does naturally in practice) with the end distal to the vein at a higher level than the proximal end, as a perfect bubble trap stopping all small bubbles of air which may enter either by a small leak in the mechanism of the tap or by some imperfection of the syringe, or by some other mishap in the course of the operation. This tube must be of a bore wide enough to allow the fluid to pass around the bubble of air instead of driving it before it, as would happen with a small tube. It can easily be made by drawing out a test-tube so as to make each end fit the small-bore rubber tubing employed while leaving a small part in the centre with the original bore.

4. Between the syringe and the fluids which are to be injected there is arranged a small glass wool filter, which effectually serves to stop all particles which may, by some mischance, be present in these fluids from entering the veins and so preventing all chance of embolism by particles of

[1] Münchener Medicinische Wochenschrift, September, 1910.

foreign matter. These filters are made by blowing a small bulb in a piece of glass tubing and packing this with glass wool. Before use the first time it is well to run water through this filter to remove all small loose pieces of glass wool.

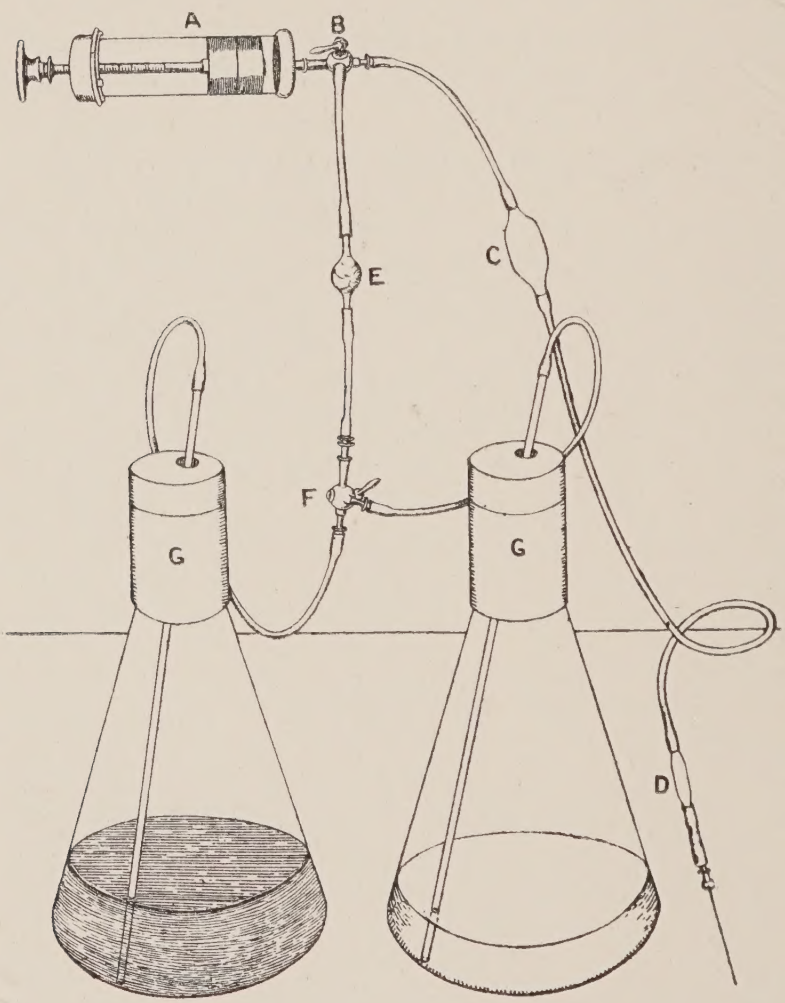
5. Two three-way taps are used (or one four-way tap), so that there is no changing of the tubes from one receptacle to the other during the operation.

The salvarsan is dissolved and made up for use exactly according to the directions enclosed with each packet of the drug, the solutions used being, of course, sterile. The amount of the fluid having been made up to 300 c.c. for the whole 0·6 grm. in a graduated vessel, the amount which it is wished to inject is poured into an Ehrlenmeyer flask ready for injection. The salt solution is conveniently made up in a similar flask, and both these flasks are fitted with double nickel caps (G in diagram), with eccentric holes just large enough to admit the delivery tubes, and these holes coincide in position or not as the outer cap is rotated, so that before the delivery tubes are in position they completely cover the opening of the flask and thus prevent contamination, and when the tubes are in position, and the drug is being administered, the opening is the smallest possible. Ehrlenmeyer flasks were adopted because they were convenient, cheap, and easy to sterilise.

It is desirable that once the apparatus has been fitted up and the solutions made, there should be no changing of the tubes from one receptacle to another. Such changing is a nuisance in the middle of the operation, and at the same time increases the liability to bacterial contamination. It can be avoided in two ways: (1) By having instead of a three-way tap a four-way tap with tubes leading direct to the flasks of salt solution, and "606," so that with different positions of the tap "606" and salt solution respectively may be drawn into the syringe and so expelled into the vein; and (2) by having the syringe connected directly with a three-way tap, so that one tube leads to the vein and the other to the solutions it is wished to inject. This latter has inserted in it another three-way tap, so that the tube is made to bifurcate, one branch going to the salt solution and the other to the "606." This second arrangement is the one we find most convenient in practice. The accompanying diagram

illustrates the apparatus which is required, and which may be described as follows:—

A 20 c.c. "Record" syringe (A) connected with a three-way tap (B). From one limb of this tap there is a piece



of rubber tubing 3 inches in length, then a glass bulb (the bubble catcher (C)), then about 15 inches of rubber tubing connected at the lower end into a metal fitting for an ordinary "Record" needle. Close to the needle in this long rubber tube there is a small piece of glass

tube let in as a window (D). The side limb of the tap is connected by a piece of rubber tubing about 3 inches long with the glass wool filter (E) which is joined by a piece of tubing 6 inches long, to another three-way tap (F), the limbs of which are, in their turn, connected by about 6 inches of tubing to 6-inch lengths of 5 mm. glass tubing. When in use these are placed, one in the flask of salvarsan and the other in the salt solution. Before use the whole apparatus must be filled with salt solution so as to avoid the danger of pushing air into the vein. This is easily done when the tubes are in position, and before the needle is inserted into the vein, by arranging the taps so that the syringe is in communication with the salt solution. The syringe is then filled, and the salt solution is expelled into the two other tubes in turn by altering the position of the taps. More salt solution is drawn up until the syringe is half full. The apparatus being filled with salt solution the needle is inserted into a vein. One can easily see when this has been accomplished by exerting a little suction so that blood appears in the glass window close to the needle. The bandage is taken off and the salt solution which is in the syringe is then expelled through the needle, and it is important here to be sure that all the fluid goes into the vein and does not leak into the surrounding tissues, as if such a leak is not noticed and some of the salvarsan solution is injected around the vein considerable pain and swelling may ensue. The taps are now altered so that the syringe is in communication with the salvarsan, and this fluid is sucked up into the syringe and expelled into the vein. This process is repeated until the whole of the salvarsan is injected, when the tap is altered once more, so that salt solution is sucked up and injected. About 40 c.c. of this should be injected after the salvarsan solution, so as to wash out the remains of the drug from the tube between the syringe and the needle, and to wash out the portion of the vein proximate to the needle in order to avoid the possible danger of phlebitis. The needle having been withdrawn, a small collodion dressing is all that is required. The best vein to select is one of those at the bend of the elbow. The skin over the vein can very easily be sufficiently sterilised with a drop of pure lysol washed off quickly with methylated spirit. Care must be taken when inserting the needle that it does not puncture the posterior wall of the vein, otherwise when one injects the salvarsan some of it will leak out round the vein and cause

Summary of Cases Treated.

No.	Nature of lesion.	Intra-venously.	Intra-muscularly.	Result.	Wassermann reaction.
		grm	grm		
1	Tertiary ulceration of nose, progressing under very energetic mercurial treatment.	—	0·5	Practically nil.	+ 2 months after.
		0·4	—	Complete healing.	+ 5 ,, ,,
2	Secondary ulceration of throat.	—	0·5	,,	− 1 month
3	Ditto.	0·4	—	,,	− 2 weeks ,, − 4 months ,,
4	Late secondary ulceration of throat.	0·4	—	,,	− 6 weeks ,,
5	Syphilis 10 years ago. Subcutaneous nodules on arm.	0·4	—	,,	− 5 ,,
6	Syphilis 8 years ago. Eczema, ? syphilitic in origin.	0·5	—	Eczema much improved.	+ 4 months ,,
7	Secondary rash and throat. Joint pains.	—	0·4	Complete recovery. (High fever for 10 days.)	− 4 weeks ,, + 3 months ,,
8	Tertiary ulceration of scalp. Resisted mercurial treatment. (Injections of calomel.)	—	0·7	Partial healing of scalp. Node appeared on forehead and another on tibia.	− 6 weeks after first injection.
		—	0·5	Nil.	+ 10 weeks after.
		0·4	—	Complete recovery.	− 10 weeks after third injection.
9	Aged 14. Congenital gumma in sterno-mastoid, ulcer on neck.	—	0·05	Nil.	
		—	0·1	Gumma broke down.	Remained + 12 weeks after last injection.
		—	0·26	Complete healing.	
10	Late secondary rash and ulceration of legs. Laryngitis.	—	0·5	Rash and ulceration cleared up.	Not seen since 14 days after when +.
11	Congenital, aged 18, sinuses connected with knee-joint (?) Deaf.	—	0·4	Nil.	
		0·4	—	Some improvement in hearing.	+ 6 weeks after second injection

Summary of Cases Treated—(continued).

No.	Nature of lesion.	Intra-venously.	Intra-muscularly.	Result.	Wassermann reaction.
		grm	grm		
12	Tertiary ulceration of neck. (Resisted mercury.)	—	0·45	Healed in 10 days.	– 2 months after
13	Tertiary ulceration of foot.	0·4	—	Healed in 20 days.	– 4 months after.
14	Tertiary ulceration of knee. Gumma shoulder.	0·3	—	Not healed in 2 months.	Still + 2 months after.
15	Tertiary ulceration over deltoid.	0·4	—	Healed in 7 days.	Not seen since 2 weeks after. Then positive.
16	General paralysis of the insane.	—	0·4	Nil.	+ 3 months after.
17	Tertiary. Periostitis humerus, 2 years. Pain in knee with erosion of bone.	0·3	—	Pain rapidly disappeared from knee and arm.	+ 4 ,, ,,
18	Congenital. Old interstitial keratitis and ulceration of thigh. No active lesions.	0·2	—	Nil.	+ 5 ,, ,,
19	Interstitial keratitis both eyes.	0·25	—	Eyes worse for 2 weeks, and not well 2 months after.	+ 2 ,, ,,
20	Interstitial keratitis.	0·2	—	Eyes much improved in 1 week.	Not seen since 1 week after.
21	Ulceration of palate, pharynx, and larynx (congenital).	0·2	—	Complete healing.	+ 2 months after.
22	Secondary rash and throat.	0·4	—	Cleared up in 1 week.	– 6 weeks ,,
23	Ulceration of throat 18 months after infection.	—	0·5	Improvement only slight.	– ,, ,,
24	Primary chancre.	0·5	—	Cleared up in 4 days.	– 6 ,, ,,

Summary of Cases Treated—(continued).

No.	Nature of lesion.	Intra-venously.	Intra-muscularly.	Result.	Wassermann reaction.
		grm	grm		
25	Primary chancre.	0·5	—	Cleared up in 5 days.	Not seen since.
26	Chancre 9 months ago. Now no lesion but Wassermann positive.	0·5	—	—	– 6 weeks after.
27	Syphilis 5 years ago. No lesion, but Wassermann positive.	0·4	—	—	– 5 ,, ,,
28	Secondary rash and throat.	0·4	—	Cleared up in 4 days.	– 2 months after.
29	Ulcer on leg, tertiary.	0·5	—	Healed in 11 weeks.	– in 1 month.
30	Tabes. Argyll Robertson pupil. Romberg's sign, pains.	0·4	—	Pains less since 2 days after; able to work 2 hours a day longer than before.	+ 3 weeks after.
31	Tertiary ulcer on neck following operation for glands.	0·4	—	Definite but not rapid improvement.	+ 3 ,, ,,
32	Tertiary ulcer on palate.	0·4	—	Quickly healed.	+ 3 ,, ,,
33	Double interstitial keratitis.	0·2	—	Eyes much worse after.	Remains positive.
34	Iritis and granulomatous patch on skin said to be syphilitic. Wassermann reaction negative.	0·4	—	Eyes rather worse. Skin remains same.	Wassermann remains –
35	Tertiary syphilide nose and cheeks.	0·5	—	Rapid healing.	+ 2 weeks after.
36	Recurrent conjunctivitis.	0·4 0·6*	—	No relapse of eye condition in 3 months.	+ 3 months after. + 2 ,, ,, second dose.
37	Chancre, rash. Throat.	0·5	—	Cleared up completely in 6 days.	– 6 weeks after.

* Because reaction +

Summary of Cases Treated—(continued).

No.	Nature of lesion.	Intra-venously.	Intra-muscularly.	Result.	Wassermann reaction.
		grm	grm		
38	Primary chancre.	0·5	—	Cleared up in 1 week.	+ 6 weeks after.
39	Ulcer knee. Syphilis 6 years ago.	0·5	—	Cleared up in 9 days.	Not seen since 14 days after.
40	Tabes.	0·4	—	No change in 1 month.	+ 1 month after.
41	Secondary rash.	0·5	—	Disappeared in 3 days.	− 1 „ „
42	Secondary rash and throat.	0·5	—	Cleared up in 5 days.	− 6 weeks after.
43	Syphilis 6 years before, superficial glossitis.	0·5	—	Cleared up within 1 week.	+ 4 „ „
44	Tertiary ulceration palate. (Resisted mercury.)	0·5	—	Ulceration stopped and healing in 17 days. Perforation remains.	− 3 months after.
45	Chancre. Secondary rash.	0·4	—	Cleared up in 1 week.	+ 3 „ „
46	Chancre 2 years before. Gummata on scalp. Later developed hæmoptysis and gummata on face.	— 0·4	0·6 —	Nil. Everything cleared up rapidly.	Remains + 7 months after first injection and 4 months after second injection.

In all cases except where stated the reaction at the time of injection was positive.

much pain and discomfort. The needle during the operation must be kept steady in the vein so as not to scratch the walls, and this can well be done by passing a piece of strapping round the arm and the butt of the needle.

The patient should be kept in bed for a time, varying according to the violence of reaction. If there is no reaction we have been in the habit of letting them get up after about 36 hours, but where there is much rise of temperature we have kept them in bed for 24 hours after the temperature has returned to normal, except in some cases where they have

insisted in getting about earlier, and in others, particularly the earlier ones, where we kept them on their backs for a longer period for purposes of observation. Even in the few cases, however, where the patient refused to stay in bed longer than about 24 hours, or where they got about with an increased temperature, we have seen no ill-effects.

While the drug was being administered intravenously, or immediately after in some cases, there has been a feeling of fulness and throbbing in the head, which soon, however, passes off, and the patient is perfectly comfortable for some time. In an hour or two in some of the cases there was a feeling of chilliness which passed sometimes into a rigor lasting from a quarter to one hour, the temperature rising during this period. In most cases there was a rise of temperature the next day, varying from 100° to 103° F., and in some this rise persisted until the following day. In a large number of the cases, however, there was absolutely no discomfort following the injection, and the rise of temperature was either absent or very slight. Comparatively few of the patients had any sickness following the injection, and we have never observed diarrhœa as a sequela. Exceptionally we have seen in one case, the first one we injected, who had 0·4 grm. intramuscularly, persistent high fever for a week. Whether this was the result of the injection, or whether he had the fever before and the drug did not affect the temperature, is open to question, as he was injected on the afternoon of the day on which he entered the hospital, so that no observations were made on his temperature before the administration of the "606."

As regards the effect of the drug on the lesions, in almost all cases the lesions which were present at the time of administration of the drug healed up with considerable rapidity. The first effect in some cases is that the affected part shows a local reaction, swelling up slightly and becoming red and irritable. This soon passes off and the healing process in most cases is very rapid. The results with the intravenous inoculations seem to be much more rapid than with the intramuscular ones, and 24 hours afterwards one can in some cases see a very distinct improvement.

In one case, after a dose of 0·7 grm. into the buttock, the lesion present, a large ulcer on the scalp which had resisted mercurial treatment, rapidly showed signs of healing, but a few days after a node appeared on the forehead, and later one on the tibia, which had the appearance of typical

syphilitic manifestations, the original ulcer all the time diminishing in size. Another intramuscular injection did not clear up the lesions, but after 0·4 grm. intravenously all the lesions rapidly disappeared, and had not recurred four months later.

In another case where there was ulceration of the nasal septum, the only effect of an injection of 0·5 grm. into the buttock, apart from the pain which it caused to the patient, was that the ulcerative process continued with greater activity. In this case also a second dose was given intravenously, with the result that the condition improved very markedly, the ulcerative process was stopped, and healing was complete.

The effect of the drug on the Wassermann reaction seems to be variable. In some of the cases where the lesions all cleared up the reaction became negative in a time varying from 2 to 12 weeks after the injection, but in one or two of those cases in which it disappeared it subsequently came back. In other cases the reaction continued to be positive months after the injection. It is important that this should be remembered in view of the very widely circulated statements that one dose of the drug is sufficient to cure syphilis, a belief which very many of the patients seem to have acquired.

We append a summary of the cases treated, stating in each case the result of the last observation made as regards the clinical condition of the patient and the Wassermann reaction.

Whether the new drug will displace mercury in the treatment of syphilis remains to be seen, and we do not venture to express any opinion on this subject. It, however, certainly has a remarkable effect in causing the lesions to disappear, and especially is this seen in some cases which have resisted mercurial treatment. Much has been made of the dangers inherent in the administration of the drug, but so far as we have gone we have not seen the slightest trace of the evil effects which have been written about in any case which has been injected intravenously.

In conclusion, we would like to thank our chief, Sir Almroth Wright, for the great help he has given us in carrying out the work in his wards at St. Mary's Hospital.